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Age-related changes in the structure and function of prefrontal cortex–amygdala circuitry in children and adolescents: A multi-modal imaging approach

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ABSTRACT

The uncinate fasciculus is a major white matter tract that provides a crucial link between areas of the human brain that underlie emotion processing and regulation. Specifically, the uncinate fasciculus is the major direct fiber tract that connects the prefrontal cortex and the amygdala. The aim of the present study was to use a multi-modal imaging approach in order to simultaneously examine the relation between *structural* connectivity of the uncinate fasciculus and *functional* activation of the amygdala in a youth sample (children and adolescents). Participants were 9 to 19 years old and underwent diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI). Results indicate that greater structural connectivity of the uncinate fasciculus predicts reduced amygdala activation to sad and happy faces. This effect is moderated by age, with younger participants exhibiting a stronger relation. Further, decreased amygdala activation to sad faces predicts lower internalizing symptoms. These results provide important insights into brain structure–function relationships during adolescence, and suggest that greater structural connectivity of the uncinate fasciculus may facilitate regulation of the amygdala, particularly during early adolescence. These findings also have implications for understanding the relation between brain structure, function, and the development of emotion regulation difficulties, such as internalizing symptoms.

Introduction

Successful social functioning requires the development of processes related to perceiving, interpreting, and appropriately responding to the emotional signals expressed on others' faces. Indeed, abnormal emotion processing is associated with a range of psychiatric disorders (Monk, 2008; Phillips et al., 2003; Pine, 2007). Because the neural circuitry associated with emotion processing undergoes substantial change during childhood and adolescence (Nelson et al., 2005), youth may be a time when sensitivity of this circuitry to genetic and environmental influences is increased. Understanding the structure and function of neural networks involved in emotion processing in childhood and adolescence will be an important step in understanding the development of emotion processing and how abnormalities arise (Cicchetti and Dawson, 2002; Hyde et al., 2011; Swartz and Monk, in press).

Theoretical frameworks have identified several key neural networks that play a role in emotional face processing (Burnett et al., 2011; Haxby et al., 2002; Nelson et al., 2005; Scherf et al., 2012). The "core" face processing network, composed of the fusiform gyrus, inferior occipital cortex, and posterior superior temporal sulcus (STS), is involved in the perceptual processing of faces (e.g., recognizing a stimulus as a face). In addition, emotional face processing consistently activates regions in limbic and prefrontal areas associated with evaluating and regulating responses to emotional stimuli (sometimes referred to as "extended" face processing regions), including the amygdala, orbitofrontal cortex, ventrolateral prefrontal cortex, and anterior cingulate cortex (Fusar-Poli et al., 2009; Tahmasebi et al., 2012).

The extended face processing circuitry comprising the amygdala and prefrontal cortex is of particular interest for the development of socio-emotional function, given its role in interpreting and regulating responses to emotional faces. Ventral regions of the prefrontal cortex receive signals from the amygdala and send signals to regulate the amygdala through direct white matter pathways, including the uncinate fasciculus, one of the major white matter tracts connecting the frontal

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lobe with the temporal lobe and limbic system (Petrides and Pandya, 2002). Diffusion tensor imaging (DTI) measures the microstructural properties of white matter tracts (Thomason and Thompson, 2011), which we refer to as structural connectivity. One of the most frequently examined measures of structural connectivity is fractional anisotropy (FA) or the degree to which water molecules diffuse along one direction, which may relate to myelination, fiber organization, or axonal packing (Beaulieu, 2002). Higher FA is interpreted as indicating greater structural connectivity between regions.

Studies conducted in adults that have combined DTI and functional MRI (fMRI) suggest that structural connectivity of the uncinate fasciculus is related to activation as well as connectivity within prefrontal cortex–amygdala circuitry. In particular, FA within this white matter region has been shown to relate to amygdala activation to fearful faces (Kim and Whalen, 2009), and functional connectivity between the anterior cingulate cortex and amygdala during emotion processing (Tromp et al., 2012). These results suggest that, for adults, greater structural connectivity within the uncinate fasciculus may facilitate communication between the prefrontal cortex and amygdala, supporting prefrontal regulation of amygdala activity (Tromp et al., 2012). However, because brain structure and function undergo substantial changes during the periods of childhood and adolescence, it is still not known how structural connectivity relates to prefrontal cortex–amygdala function in early life.

Longitudinal and cross-sectional studies of the uncinate fasciculus generally demonstrate a pattern of increased FA with advancing age across childhood and adolescence (Lebel and Beaulieu, 2011; Lebel et al., 2008). Longitudinal studies have also demonstrated variability in individual trajectories, with some individuals demonstrating increases, decreases, or maintained levels of FA in this tract over time (Lebel and Beaulieu, 2011). Given prior observed variance in white matter integrity in youth, it is possible that developmental variation in white matter could be associated with differences in brain function or psychosocial outcomes.

Several fMRI studies have demonstrated age-related changes in neural activation associated with emotional face processing across childhood, adolescence, and adulthood. For instance, in a large cross-sectional study with participants ranging in age from 4 to 22 years old, Gee et al. (2013) demonstrated a linear decrease with age in amygdala activation to fearful faces. Other studies have demonstrated greater amygdala activation to emotional faces in adolescents relative to adults (Guyer et al., 2008; Hare et al., 2008; Monk et al., 2003; Passarotti et al., 2009). Research focusing strictly on child and adolescent samples has also shown changes in emotion processing associated with development. These changes include increased amygdala response to sad faces with age during early adolescence (Pfeifer et al., 2011), as well as decreased amygdala activation to neutral faces and decreased ventrolateral prefrontal cortex activity to fearful faces with pubertal development (Forbes et al., 2011). Overall, these results suggest a complex, non-linear pattern of development dependent on the nature of the emotion processing task and emotional stimuli used, with the most consistent trend indicating that amygdala activation to emotional faces decreases from adolescence to adulthood.

There is also emerging evidence for changes in prefrontal cortex–amygdala functional connectivity from childhood to adulthood. Using a psychophysiological interaction analysis, Gee et al. (2013) demonstrated a shift in the direction of functional connectivity from childhood to adulthood with the youngest age group (4 to 9 years old) exhibiting positive amygdala–rostral anterior cingulate connectivity while viewing fearful faces whereas older participants evidenced negative functional connectivity that grew stronger with age. This shift from positive to negative connectivity was suggested to reflect increased prefrontal regulation of amygdala activation with age. Another study implementing a correlational functional connectivity analysis found that across children, adolescents, and adults, the amygdala was negatively connected with the ventral prefrontal cortex during an emotional face go/no go task and the strength of connectivity related to greater amygdala habituation (Hare et al., 2008). However, although the amygdala and ventral prefrontal cortex showed differences in activity across the three age groups, changes in connectivity with age were not directly tested. A different study by Guyer et al. (2008) directly compared functional connectivity across adolescents and adults, and reported no difference in connectivity between prefrontal and amygdala regions between groups during emotion processing, indicating that these effects may be dependent on the task performed or the functional connectivity analytical approach.

All together, research that examines amygdala function and connectivity in early life has shown that structural and functional connectivity between the prefrontal cortex and amygdala increases with age and amygdala activation to emotional faces decreases with age across childhood and adolescence. Though generally examined separately, it is important to consider brain structure and function simultaneously when examining development, as it is possible that changes in brain structure constrain changes in function, or vice versa (Cicchetti and Dawson, 2002). Moreover, it is important to include behavioral measures in order to examine how changes in brain structure and function relate to emotion regulation. The only study yet to examine these relations in an adolescent sample used event-related potentials (ERPs; Taddei et al., 2012). Taddei et al. (2012) found that N400 ERP amplitudes (a response evoked by viewing emotional faces) to angry faces measured at ages 8–9 negatively predicted FA in the left uncinate fasciculus at ages 14–15. Moreover, scores on a measure of harm avoidance collected during childhood negatively predicted right uncinate fasciculus FA values in adolescence. These results demonstrate that neural activity in response to processing faces is related to structural connectivity of the uncinate fasciculus; however, because of the use of ERPs in this study, the relation between uncinate fasciculus structural connectivity and amygdala activation or functional connectivity during adolescence remains untested.

The objective of the present study was to examine the relation between structural connectivity of the uncinate fasciculus, functional activation and connectivity of prefrontal cortex–amygdala circuitry, and a measure associated with emotion regulation difficulties (internalizing symptoms) during the periods of late childhood and adolescence. Our first hypothesis was that greater structural connectivity of the uncinate fasciculus would predict reduced amygdala activation to emotional faces. Second, we hypothesized that increased structural connectivity of the uncinate fasciculus would predict greater functional connectivity between the amygdala and prefrontal cortex. Third, we hypothesized that increased functional connectivity would predict decreased amygdala activation to emotional faces. Fourth, we hypothesized that greater structural and functional connectivity, as well as decreased amygdala activation, would predict lower internalizing symptoms. Fifth, we examined whether the brain structure–function relationship was moderated by age. Because this circuitry is undergoing development during childhood and adolescence, the strength of the relationship between brain structure and function may differ across this age range.

Methods

Participants

Participants were recruited from the community through fliers. Parents reported that participants had no history of psychiatric diagnoses. Moreover, all participants were below the clinical cutoff score for internalizing symptoms on the Child Behavior Checklist (CBCL; Achenbach and Rescorla, 2001). Participants 18 years and older provided informed consent; minor participants gave assent and their parents signed informed consent forms. A total of 79 participants between 8 and 19 years of age underwent fMRI scanning. Nineteen participants were removed from analyses due to: movement >3 mm in any direction (4 participants), technical problems during scanning (2 participants), accuracy <70% on the behavioral tasks (2 participants), poor normalization or signal dropout within the amygdala or prefrontal cortex (10 participants), and showing elevated scores on a measure of autism